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Current Clinical Trials in paediatrics: report of the ESPEN Special Interest Group in Paediatrics

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2 **Abstract**

3 **Background & Aims:** At the 38th annual ESPEN congress in The Hague, the Netherlands, the
4 Special Interest Group (SIG) in Paediatrics presented data about current research activities in
5 the field of paediatric nutrition which are performed worldwide and translated this to future
6 research perspectives.

7 **Methods:** Extensive search of all registered observational and interventional clinical trials in
8 the database ClinicalTrials.gov using the search terms: children nutrition, paediatrics
9 nutrition and children feeding.

10 **Results:** A total of 717 studies were found; 173 were duplicates and 114 included adult
11 participants and were therefore excluded. Hence, 430 remained for analysis, of which 69%
12 were randomized controlled trials. The most investigated research topic was nutrition in
13 specific diseases (n=98), followed by obesity (n=92), and studies including premature infants
14 (n=48). The overall median estimated enrolment of children in the trials was 150 children
15 [IQR 50 - 365]. There were 44 studies in which >1,000 participants will be enrolled and six
16 studies with >10,000 participants. Studies including >1,000 participants were primarily
17 performed in North America (39%), Africa (27%), and Europe (16%).

18 **Conclusions:** This SIG report showed that 430 clinical nutrition trials in paediatrics are
19 registered and current research focusses primarily on specific diseases and obesity. The SIG
20 paediatrics encourages future research to invest in well-controlled interventional trials.

1. Introduction

In September 2017 at the 38th European Society for Clinical Nutrition and Metabolism (ESPEN) congress in The Hague, the Netherlands the ESPEN special interest group (SIG) in Paediatrics had its annual meeting. One of the objectives of SIG Paediatrics is to coordinate, promote, or develop research projects or programs of studies in clinical nutrition in hospitalized and outpatient children and to develop position statements (1). The aim of the current manuscript is to report about ongoing paediatric research activities worldwide, which are registered in ClinicalTrials.gov and discuss future research activities that might be useful.

2. Methods

To gain an overview of all the current trials performed in the field of clinical nutrition in paediatrics the website ClinicalTrials.gov was used. The website provides the ability to find individual trials, but also search for them using certain terms. The following three search terms were entered in the search field: “Children AND Nutrition”, “Paediatrics AND Nutrition”, and “Children AND Feeding”. Trials were included in this search if: 1) Participants were children in the age range 0-18 year; 2) Design of the trial was intervention and/or observational 3) Status of trial was recruitment or pre-recruitment. No limits were selected with regard to gender, study results, study phase and funder type. Data acquisition was completed on 8th of August 2017 prior to the ESPEN annual meeting.

Data collected for subsequent analysis were the start and (expected) completion date of primary outcome, title, study type, study design, estimated enrolment number, gender, minimum and maximum age, sponsor, country where research is performed and number of

centers included. The investigators of the registered trials need to select the condition, usually the main topic or disease, in which their research is performed. For example, an investigator was interested in undernutrition within Crohn's disease. When registering the trial the investigator need to select a condition (topic or disease field), which can either be undernutrition or Crohn's disease in this example. Therefore, conditions from ClinicalTrials.gov were based on what the investigators of the trials found the most important and suitable condition for their research. We collected the conditions of the investigators and used them to classify the main topic of the trials in our database, which was performed by one observer (RE). The trial characteristics were summarized and reported as counts and percentages.

3. Results

With applying the three search terms, 717 studies were found, out of which 173 were duplicates and 114 included adult populations and were therefore excluded (**Fig. 1**). Hence, 430 studies were brought forward for further analysis. Sixty-nine percent of the studies were randomized controlled trials (RCT), 18% non-randomized intervention trials and 13% observational studies. Most of the studies were performed in North America (49%), Europe (24%) and Asia (17%) (**Table 1**); 53% of the studies were single center research. The studied population consisted only of infants in 25% and only adolescents in 2% of the studies. The expected date of study completion was for 213 studies in 2017 and 10 in 2018.

Fifteen different research topics were identified within paediatric nutrition research. The most investigated research topic was nutrition in specific diseases (n=98), followed by obesity (n=92), and studies including premature infants (n=48) (**Fig. 2**). Obesity and

undernutrition combined accounted for 27% (n=116) of all research. Studies related to obesity were predominantly performed in North-America (67%) and Europe (23%), whereas studies regarding undernutrition in the general population were performed in Africa (50%) and Asia (28%). Hospital undernutrition was mostly investigated in Asia (68%) and undernutrition resulting from anorexia nervosa in Europe (100%). Trials investigating obesity were mostly based on educational, nutritional or exercise intervention (n=80). (Epi)genetics, altered pharmacokinetics and development were also investigated.

A total of 98 studies investigated nutrition within specific diseases, of which 30 were performed in gastrointestinal diseases, such as Crohn's disease (n=10), inflammatory bowel disease (n=5), and short bowel syndrome (n=2). Other investigated areas were children with respiratory diseases (n=11) and neurological conditions (n=10) (**Fig. 3**). The median estimated number of participant enrolment was 150 children [IQR 50 - 365]. There were 44 studies in which $\geq 1,000$ participants will be enrolled and six studies with $>10,000$ participants. Studies including $\geq 1,000$ participants were primarily performed in North America (39%), Africa (27%), and Europe (16%). The three largest nutrition RCT were: 1) a double-blind RCT on antibiotics for children with severe diarrhoea in Kenya; 2) a RCT investigating the impact of promoting community initiated kangaroo mother care for low birth weight Infants in India; 3) a single arm RCT investigating a nutritional care program and psychosocial stimulation to improve malnourished children's development in Bangladesh.

4. Discussion

This analysis of the currently ongoing clinical trials worldwide showed that most reported studies were randomized clinical trials, in single centers and performed predominantly in

North America. The major research topics registered were obesity and disease specific nutrition. Interestingly within the topic obesity, most studies concerned behavioural nutritional interventions and within the topic disease specific most studies were related to gastrointestinal diseases.

Last year the ESPEN Paediatric SIG reported that it was an important priority to test hypotheses generated from association studies within well-controlled trials and explore the effectiveness of nutritional interventions in improving patients' clinical outcomes and disease prognosis (1). Therefore, we were within this study primarily interested in well-designed and adequately powered RCT's. Unfortunately, information on power calculations were not presented on ClinicalTrials.gov. Nevertheless, to present an overview of relevant RCT's which are likely to influence future guidelines we decided to display large trials with an arbitrary cut-off value of 1,000 participants. First, it was remarkable that large RCT's were relatively more performed in low and medium income countries. The three largest trials were performed in Kenya, India and Bangladesh. Secondly, we could identify only a limited number of large RCT's which might have an impact on the development of clinical guidelines and three upcoming trials should be highlighted. First, the long-term follow up of the PEPaNIC study investigating the effect of supplemental parenteral nutrition on long-term neurocognitive outcome in critically ill children. Second, a RCT on the induction of early solids foods on the food tolerance in babies, and third, a nurse-led parent educational support intervention for discharged children with newly diagnosed cancer.

The impact of the results of these ongoing studies in children is yet unknown. Recently, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), the European Society of Paediatric Research (ESPR) and ESPEN have jointly developed new guidelines for paediatric PN (2), while ESPGHAN and the European Society of

Paediatric and Neonatal Intensive Care (ESPNIC) are developing joint guidelines for nutrition in paediatric intensive care. In both guideline development processes it became obvious that there is a lack of high quality controlled nutritional interventional studies on important unresolved questions. An example of a published interventional study which will have an impact on the new guidelines is the multicenter PEPaNIC trial (3). This study showed that initiating parenteral nutrition (PN) after one week of critical illness as compared to starting on the first day of paediatric intensive care reduced newly acquired infections and accelerated recovery, with a shorter duration of mechanical ventilation and stay on the paediatric intensive care and in the hospital. However, there was a significant increased risk of developing hypoglycemia and therefore follow-up research is needed before definitive recommendations can be made (4, 5). New guidelines will take the results of the PEPaNIC study into account. Additional research is needed to more accurately determine the dosing and timing of administration of PN in critical illness. Another future research of interest in critically ill children is the amount of EN in relation with periods of fasting and the circadian rhythm.

There is an unmet need for more studies exploring the role of nutritional interventions and how this can improve, not only nutritional, but also clinical outcomes in healthy children and in patients with different disorders. While there is substantial evidence exploring nutritional support in adult (mainly geriatric) patients (6-8), there appears to be a staggering lack of evidence from paediatric studies. Such interventions can span from diagnostic evaluation to therapeutic interventions such as dietary counselling, food fortification, supplementation with oral nutritional supplements and enteral and parenteral nutritional support. In these studies the effects of energy providing nutrients and micronutrients can be studied together or separately. The hypotheses tested in clinical trials

should ideally be backed up by data from preclinical and mechanistic studies, which are currently also frequently lacking.

There are some limitations of our survey. In this analysis we only used the ClinicalTrials.gov database. This database is run by the United States National Library of Medicine and was the first online registry for clinical trials and is the largest and most widely used today. There are other databases which can be screened as well, such as EU register, JPRN, ISRCTN, ANZCTR, but we did not incorporate these databases (9). We included observational and interventional trials, but only 13% of the registered trials were observational trials. Registration of interventional trials has become a prerequisite for publication in leading peer-reviewed journal, which possible resulted to a bias in our database.

In conclusion, in this SIG report it was shown that 430 clinical nutritional trials in paediatrics are currently registered with predominant focus on obesity and gastrointestinal diseases. There is need for more high quality, controlled intervention trials in paediatric nutrition.

Statement of authorship

RE and KJ collected and analysed the data. RE, KJ and KG drafted the first manuscript. All authors contributed to the data interpretation and revised the manuscript. All authors approved the final manuscript.

Conflicts of interest statement and funding sources

RE received a grant from Nutricia Research B.V., Utrecht, The Netherlands. Nutricia Research B.V. was not involved in the collection, analysis or interpretation of the data, nor were they involved in the decision to publish the results.

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Abbreviations

ESPEN: European Society for Clinical Nutrition and Metabolism; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; ESPNIC: European Society of Paediatric Neonatal Intensive Care; ESPR: European Society of Paediatric Research; PN: parenteral nutrition; RCT: randomized controlled trials; SIG: Special interest group

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200 Journal Editors' policy of mandatory, timely clinical trial registration. J Am Med Inform Assoc.
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202 **Table 1.** Geographic location of performed research within paediatric clinical nutrition.

Continents		Top 6 Countries	
North-America	49%	United States	40%
Europe	24%	Canada	8%
Asia	17%	France	5%
Africa	7%	Israel	4%
South-America	2%	China	4%
Australia	1%	Bangladesh	3%

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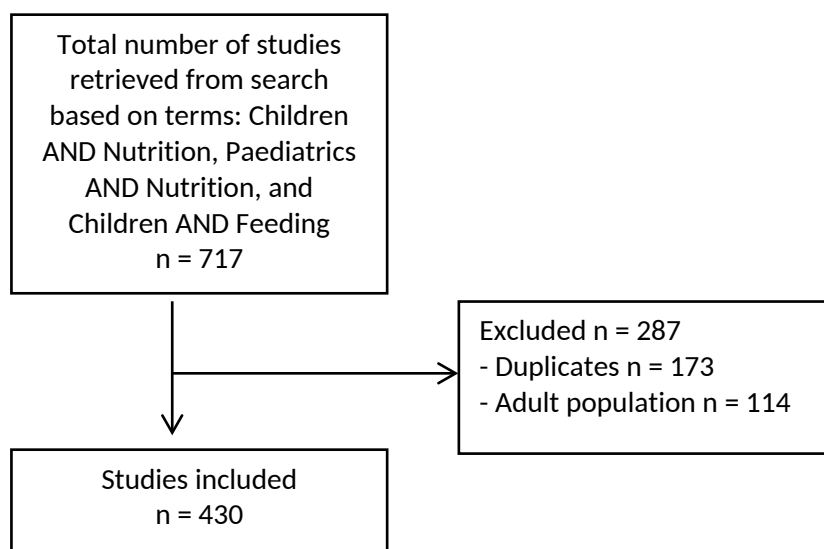


Fig. 1. Flowchart of search for clinical nutrition studies in children using database of ClinicalTrials.gov.

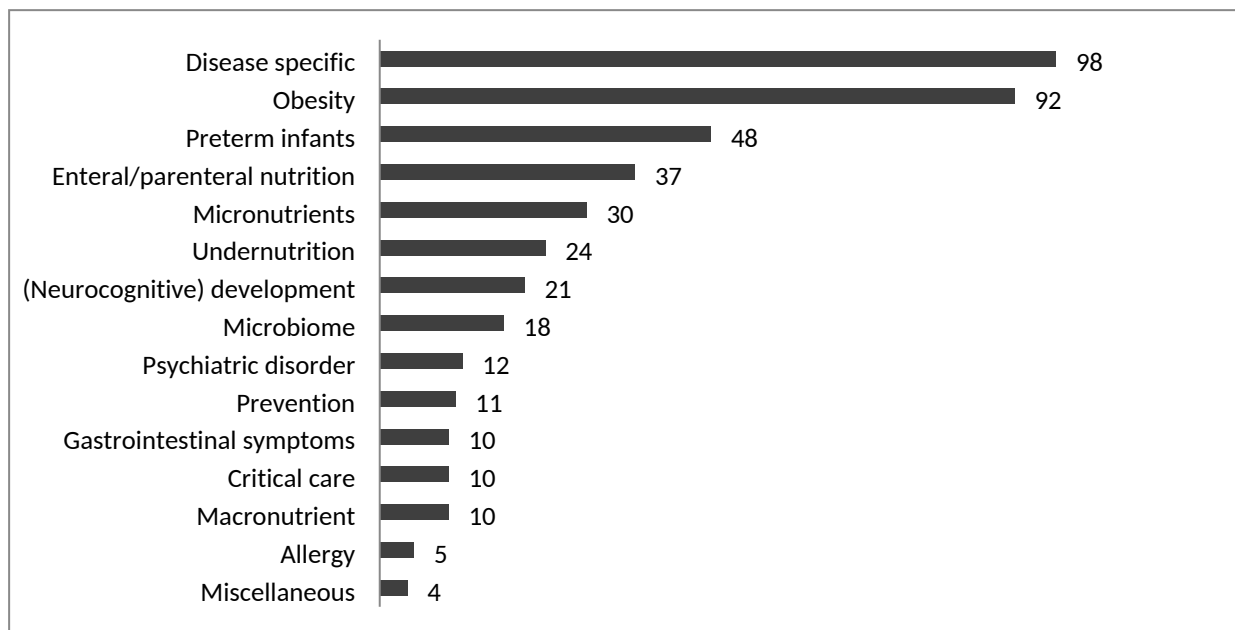


Fig. 2. Number of studies according to topics within paediatric clinical nutrition research (retrieved from ClinicalTrials.gov up to August 8th 2017)

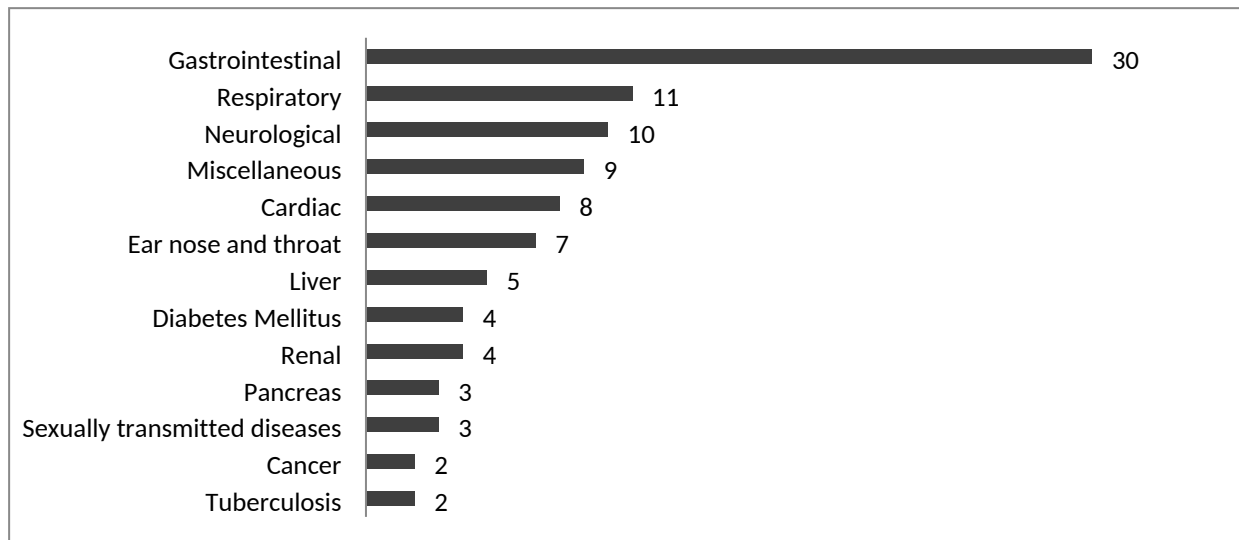


Fig. 3. Disease specific topics within paediatric clinical nutrition research (total number = 98; retrieved from ClinicalTrials.gov up to August 8th 2017)